

Date of Approval: May 21, 2020

CORRECTED FREEDOM OF INFORMATION SUMMARY

ORIGINAL ABBREVIATED NEW ANIMAL DRUG APPLICATION

ANADA 200-680

Enrofloxacin Flavored Tablets

(enrofloxacin)

Dogs and Cats

Enrofloxacin Flavored Tablets are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enrofloxacin Flavored Tablets are indicated for use in dogs and cats.

Sponsored by:

Felix Pharmaceuticals Pvt. Ltd.

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I. GENERAL INFORMATION

A. File Number

ANADA 200-680

B. Sponsor

Felix Pharmaceuticals Pvt. Ltd.
25–28 North Wall Quay
Dublin 1, Ireland

Drug Labeler Code: 086101

U.S. Agent Name and Address:
James H. Schafer, DVM
Schafer Veterinary Consultants, LLC
800 Helena Court
Fort Collins, CO 80524

C. Proprietary Name

Enrofloxacin Flavored Tablets

D. Drug Product Established Name

enrofloxacin

E. Pharmacological Category

Antibacterial

F. Dosage Form

Flavored Tablet

G. Amount of Active Ingredient

22.7 mg, 68 mg, and 136 mg enrofloxacin per tablet

H. How Supplied

22.7 mg in 100 and 500 tablet bottles
68 mg in 50 and 250 tablet bottles
136 mg in 50 and 200 tablet bottles

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Dogs: Administer orally at a rate to provide 5-20 mg/kg (2.27 to 9.07 mg/lb) of body weight. Selection of a dose within the range should be based on clinical experience, the severity of disease, and susceptibility of the pathogen. Animals which receive doses in the upper-end of the dose range should be carefully

monitored for clinical signs that may include inappetence, depression, and vomition.

Weight of Dog	Once Daily Dosing Chart			
	5.0 mg/kg	10.0 mg/kg	15.0 mg/kg	20.0 mg/kg
9.1 kg (20 lb)	2 X 22.7 mg tablets	1 X 22.7 mg plus 1 X 68 mg tablets	1 X 136 mg tablet	1 X 136 mg plus 2 X 22.7 mg tablets
27.2 kg (60 lb)	1 X 136 mg tablet	2 X 136 mg tablets	3 X 136 mg tablets	4 X 136 mg tablets

Cats: Administer orally at 5 mg/kg (2.27 mg/lb) of body weight.

Weight of Cat	Once Daily Dosing Chart (5 mg/kg/day)
5 lb (2.27 kg)	½ X 22.7 mg tablet
10 lb (4.5 kg)	1 X 22.7 mg tablet
15 lb (6.8 kg)	1 and ½ X 22.7 mg tablets or ½ X 68 mg tablet

The dose for dogs and cats may be administered either as a single daily dose or divided into two (2) equal daily doses administered at twelve (12) hour intervals. The dose should be continued for at least 2-3 days beyond cessation of clinical signs to a maximum of 30 days.

K. Route of Administration

Oral

L. Species/Class

Dogs and cats

M. Indication

Enrofloxacin Flavored Tablets are indicated for the management of diseases associated with bacteria susceptible to enrofloxacin. Enrofloxacin Flavored Tablets are indicated for use in dogs and cats.

N. Reference Listed New Animal Drug (RLNAD)

Baytril® Taste Tabs®; enrofloxacin; NADA 140-441; Bayer HealthCare LLC, Animal Health Division

II. BIOEQUIVALENCE

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) of 1988, allows for an abbreviated new animal drug application (ANADA) to be submitted for a generic version of an approved new animal drug (RLNAD). The ANADA sponsor is required to show that the generic product is bioequivalent to the RLNAD, which has been shown to be safe and effective. Effectiveness, target animal safety and human food safety data (other than tissue residue data) are not required for approval of an ANADA. If bioequivalence is demonstrated through a clinical endpoint study in a food producing

animal, then a tissue residue study to establish the withdrawal period for the generic product is also required.

For this ANADA, two *in vivo* blood-level studies were conducted to demonstrate product bioequivalence, using the generic and RLNAD enrofloxacin 22.7 mg tablet in cats and the 136 mg tablet in dogs. The RLNAD is available in 22.7, 68, and 136 mg tablet sizes. The *in vivo* blood-level studies were conducted in 24 healthy, fasted beagle dogs and 24 healthy, fasted cats. There were no serious adverse events reported during either study. Bioequivalence was demonstrated between the 22.7 mg RLNAD tablets and the 22.7 mg generic enrofloxacin tablets in the cat and the 136 mg RLNAD tablets and the 136 mg generic enrofloxacin tablets in the dog by demonstrating that the confidence limits for the difference between the pivotal parameters C_{MAX} and AUC are contained within the equivalence limits of 80.00% and 125.00%.

A waiver from the requirement to demonstrate *in vivo* bioequivalence (biowaiver) for the generic 22.7 mg, 68 mg, and 136 mg tablets was requested. Dissolution data was used to demonstrate that the generic 22.7 mg, 68 mg, and 136 mg enrofloxacin tablets are comparable to the generic 22.7 mg and 136 mg tablet strengths used in the *in vivo* blood-level bioequivalence studies. Therefore, a biowaiver for the generic 22.7 mg and 68 mg enrofloxacin tablets in dogs, and the 68 mg and 136 mg generic enrofloxacin tablets in cats was granted. The study information is summarized below.

A. Blood-Level Bioequivalence Study in Dogs

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of enrofloxacin tablets (136 mg).

1. Study Title:

Pivotal Bioequivalence Study of BAYTRIL® Tablets and a Generic Formulation of Enrofloxacin when Administered Orally to Beagle Dogs

2. Protocol:

A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of the generic 136 mg enrofloxacin tablet in 24 healthy, fasted dogs.

3. Testing Facilities:

In-life phase: Ontario, Canada
Bioanalytical testing: Middleton, WI.

4. Study Number:

Test Facility Study Number: KFI-080-BC-0516
Sponsor Study Number: ENRH-KC2-0217

5. Objective:

The objective of this study was to assess the pharmacokinetics and *in vivo* bioequivalence of test article (generic enrofloxacin tablets) compared to the

reference article (Baytril® enrofloxacin tablets) using a two-period, two-sequence crossover design in dogs.

6. Measurement and Observation:

The plasma concentrations of enrofloxacin were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events. No significant adverse events were recorded.

7. Statistical Methods:

The study was conducted as a randomized, two-period, two-sequence, single-dose crossover design using 24 dogs with a 7 day washout between periods. Variables evaluated are area under the concentration (AUC) curve from time 0 to the first value below the limit of quantitation and the observed maximum concentration (C_{MAX}). The statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence as a random effect. Time to maximum concentration (T_{MAX}) is also evaluated.

The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00%. As seen in the table below, both AUC and C_{MAX} fall within the prescribed bounds (Table II.1). T_{MAX} values obtained for the test product and reference product indicate that these drugs will provide equivalent therapeutic results.

Table II.1 Bioequivalence Evaluation in Dogs

Parameter	Test Mean	Reference Mean	Ratio [◇]	Lower Bound (%)	Upper Bound (%)
AUC (ng/mL)*hour	14368 [†]	14292 [‡]	1.01	87	116
C_{max} (ng/mL)	2670 [†]	2553 [‡]	1.05	93	117
T_{max} (hour)	1.5 [‡]	1.8 [‡]	NE	NE	NE

[†] Geometric mean

[‡] Arithmetic mean

[◇] Ratio = ratio geometric means (Test/Reference)

NE = not estimated

B. Blood-level Bioequivalence Studies in Cats

One blood-level bioequivalence study was conducted to determine the comparative bioavailability of the generic and RLNAD formulations of enrofloxacin tablets (22.7 mg).

1. Study Title:

Pivotal Bioequivalence Study of BAYTRIL® Tablets and a Generic Formulation of Enrofloxacin when Administered Orally to Cats

2. Protocol:
A randomized, two-period, two-sequence, single-dose crossover study to evaluate the relative bioavailability of 22.7 mg generic enrofloxacin tablets administered orally to 24 healthy, fasted cats.
3. Testing Facilities:
In-life phase: Ontario, Canada
Bioanalytical testing: Middleton, WI.
4. Study Number:
Test Facility Study Number: KFI-080-BF-0416
Sponsor Study Number: ENRH-KF2-0317
5. Objective:
The objective of this study was to assess the *in vivo* bioequivalence of the test article (generic enrofloxacin tablets) compared to the reference article (Baytril® (enrofloxacin) Taste Tabs®) in a randomized, two-period, two-sequence, single-dose crossover study in cats.
6. Measurement and Observation:
The plasma concentrations of enrofloxacin were measured using a validated bioanalytical method. Pharmacokinetic parameters were determined for each animal individually in each period. Animal observations were made throughout the study for assessment of general health and adverse events. No significant adverse events were recorded.
7. Statistical Methods:
The study was conducted as a randomized, two-period, two-sequence, single-dose crossover design using 24 purpose-bred, male and female cats with a 14-day washout between periods. Variables evaluated are area under the concentration (AUC) curve from time 0 to first value below the limit of quantitation and the observed maximum concentration (C_{MAX}). The statistical model included sequence, treatment, and period as fixed effects, and animal-within-sequence as a random effect.

The criteria for determining bioequivalence is to construct a 90% confidence interval about the difference of the two means, generic minus pioneer, based on the natural log scale of AUC and C_{MAX} and then take the anti-log of the confidence limits multiplied by 100. The resulting bounds should be between 80.00% and 125.00% for both AUC and C_{MAX} . As seen in the table below, AUC and C_{MAX} fall within the prescribed bounds (Table II.2).

Table II.2 Bioequivalence Evaluation in Cats

Parameter	Test Mean	Reference Mean	Ratio [◇]	Lower Bound (%)	Upper Bound (%)
AUC (ng/mL) *hour	13967 [†]	13752 [†]	1.02	98	105
C_{max} (ng/mL)	1549 [†]	1517 [†]	1.02	96	109
T_{max} (hour)	1.25 [‡]	1.15 [‡]	NE	NE	NE

[†]Geometric mean

[‡]Arithmetic mean

[◊]Ratio = ratio geometric means (Test/Reference)

NE = not estimated

C. Bioequivalence Waiver

Two pivotal *in vivo* blood bioequivalence studies were conducted using the 22.7 mg enrofloxacin tablet in cats and the 136 mg enrofloxacin tablet in dogs. A waiver from the requirement to perform *in vivo* bioequivalence studies (biowaiver) for the generic 22.7 mg and 68 mg for dogs, and the 68 mg and 136 mg tablets for cats was requested. To qualify for a biowaiver for each of these product strengths, comparative *in vitro* dissolution studies were conducted to determine the dissolution profiles of the Felix Pharmaceuticals PVT LTD's generic and RLNAD 22.7 mg, 68 mg and 136 mg enrofloxacin tablets. The similarity factor (f_2) calculation was used to evaluate dissolution profile comparisons. Comparisons were made between the following tablets:

- Generic 22.7 mg and RLNAD 22.7 mg tablets.
- Generic 68 mg and RLNAD 68 mg tablets.
- Generic 136 mg and RLNAD 136 mg tablets.

The objective was to satisfy f_2 criteria between the generic tablet strengths and the RLNAD tablet strengths.

Test conditions were as follows:

- Dissolution apparatus: USP Apparatus Type I, basket
- Dissolution medium: Sodium citrate buffer, pH 4.0
- Dissolution medium volume: 900 mL
- Temperature: $37 \pm 5^\circ\text{C}$
- Stirring rate: 100 rpm
- Number of vessels: 12
- Data points: 5, 10, 15, 30, and 45 minutes
- Analytical method: HPLC with UV detection

The generic and RLNAD drug lot number used in the *in vivo* bioequivalence studies (22.7 mg for cats and 136 mg for dogs) were the same lots used to support the *in vitro* profile comparisons. Analytical method validation was required to ensure that the quantification of drug concentrations in all samples was accurate and precise.

To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 15 minutes) should not be more than 20%, and at other time points should not be more than 10%. The percent coefficient of variation for all generic product profiles was within acceptable limits. Only one measurement should be considered after 85% dissolution of both products. The similarity factor (f_2) should be greater than 50 to ensure sameness or equivalence of two profiles. In cases where both the generic and RLNAD tablets are > 85% dissolved in less than 15 minutes, a dissolution profile comparison using the f_2 test is unnecessary. When comparative profiles between the test and reference products do not require an f_2 test because of rapid dissolution or when the f_2

value is ≥ 50 , the product strength used in the comparison qualifies for a biowaiver.

A summary of the results is presented in Table II.3 below:

Table II.3. Similarity (f2) Results

Dissolution Comparison	f2 (≥ 50 indicates sameness)
22.7 mg generic to the 22.7 mg RLNAD	> 85% dissolved within 15 minutes supports sameness, f2 not required
68 mg generic to the 68 mg RLNAD	> 85% dissolved within 15 minutes supports sameness, f2 not required
136 mg generic to the 136 mg RLNAD	> 85% dissolved within 15 minutes supports sameness, f2 not required

Study results demonstrate similar dissolution profiles for the generic and RLNAD 22.7 mg, 68 mg, and 136 mg enrofloxacin chewable tablets. Therefore, a biowaiver for the generic 22.7 mg and 68 mg enrofloxacin chewable tablets in dogs, and the 68 mg and 136 mg generic enrofloxacin chewable tablets in cats is granted.

III. HUMAN FOOD SAFETY

This drug is intended for use in dogs and cats. Because this new animal drug is not intended for use in food producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this ANADA.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Enrofloxacin Flavored Tablets:

For use in animals only. Keep out of reach of children.

Avoid contact with eyes. In case of contact, immediately flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water. Consult a physician if irritation persists following ocular or dermal exposure. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight.

V. AGENCY CONCLUSIONS

This information submitted in support of this ANADA satisfy the requirements of section 512(c)(2) of the FD&C Act. The data demonstrate that Enrofloxacin Flavored Tablets, when used according to the label, is safe and effective.

VI. APPENDIX

May 21, 2020 - The original study numbers under the "Blood-Level Bioequivalence Study in Dogs" section II.A.4 on page 5:

Test Facility Study Number: KFI-062-BC-1715

Sponsor Study Number: P15-026

June 15, 2020 - Revised to reflect the correct study numbers under the "Blood-Level Bioequivalence Study in Dogs" section II.A.4 on page 5:

Test Facility Study No.: KFI-080-BC-0516

Sponsor Study No.: ENRH-KC2-0217

Also, updated to current format.